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Role of NDDS in Tuberculosis Management: An Emerging Paradigm

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Abstract: *Tuberculosis (TB) remains a significant global health challenge, necessitating innovative approaches for effective treatment. Conventional TB therapy encounters several limitations, including extended treatment duration, drug resistance, patient noncompliance, poor bioavailability, and suboptimal targeting. Advanced drug delivery strategies have emerged as a promising approach to address these challenges. They have the potential to enhance therapeutic outcomes and improve TB patient compliance by providing benefits such as multiple drug encapsulation, sustained release, targeted delivery, reduced dosing frequency, and minimal side effects. This review examines the current landscape of drug delivery strategies for effective TB management, specifically highlighting lipid nanoparticles, polymer nanoparticles, inorganic nanoparticles, emulsion-based systems, carbon nanotubes, graphene, and hydro gels as promising approaches. Furthermore, emerging therapeutic strategies like targeted therapy, long-acting therapeutics, extrapulmonary therapy, phototherapy, and immunotherapy are emphasized.*

Keywords: Drug delivery systems, Extensive drug-resistant tuberculosis, Multidrug-resistant tuberculosis, Nanoparticles, Therapeutics, Tuberculosis

I. INTRODUCTION

NOVEL DRUG DELIVERY SYSTEM

A revolutionary technique that combines innovative development, formulations, new technology, and novel methodology for delivering pharmaceutical substances in the body as necessary to safely achieve their targeted pharmacological effects is known as a Novel Drug Delivery System (NDDS). It may also improve drug potency, control drug release with a sustained pharmacological effect, and scientific site-targeting throughout the body. It entails the creation of brand-new, improved, and safer medications with protracted half lives and significant therapeutic indices. In comparison to the pre-existing delivery systems.[1]

ADVANTAGES OF NOVEL DRUG DELIVERY SYSTEM

- Decreased dosing frequency.
- Decreased rate of increase in blood drug concentration.
- Blood level that is constant and sustained within the therapeutic window
- Enhanced bioavailability.
- Ability to achieve a targeted drug release.
- Reduced side effects.
- Improved patient compliance.[2]

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CONVENTIONAL DRUG DELIVERY SYSTEM:

Conventional DDS have been crucial in improving therapeutic efficacy by managing the dose, time, and location of drug release. However, traditional systems lacked control over drug release, leading to inefficiency in drug absorption and distribution. To address such limitations, advancements such as coated technology and enteric coatings were established, improving drug stability and release patterns. Regardless of these advancements, conventional DDS still suffer from limitations such as poor bioavailability, non-specific targeting, and unwanted side effects.[3]

LIMITATIONS OF CONVENTIONAL DRUG DELIVERY SYSTEM:

One key disadvantage is reduced bioavailability, especially for orally administered drugs, where first-pass metabolism and the rate of drug elimination can reduce the drug delivery to systemic circulation considerably This often results in suboptimal therapeutic effects, necessitating higher doses to establish the desired response. Another major issue is non-specific targeting, wherein drugs spread across the body instead of being active only at the desired loca tion. This indiscriminate distribution can result in undesirable side effects and potential toxicity in off-target tissues, restrict ing the safety and accuracy of treatment.[4]

TUBERCULOSIS (DISEASE):

Tuberculosis is an infectious disease that has more than 1 million cases per year in India. It is caused by bacteria Mycobacterium tuberculosis. Generally, it affects the pulmonary portion of the human body, but it can also affect other parts if it remains untreated. In 1990, the World Health Organisation (WHO) concluded on the Global Burden of disease that TB is the seventh most fatal disease in the world.[6]

Although TB control has been effective in some world regions, these gains are threatened by the increasing burden of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. XDR-TB has evolved in several tuberculosis-endemic countries to drug-incurable or pro grammatically incurable tuberculosis (totally drug-resis tant tuberculosis).[7]

PATHOGENESIS OF TUBERCULOSIS:

The majority of droplet nuclei containing MTB from infectious patients are trapped in upper airway and expelled by ciliated mucosal cells: only a fraction reaches alveoli. The mycobacteria then bind to cell surface of alveolar macro phages through complement receptors, mannose receptor or type A scavenger receptor. Following phagocytosis, myco bacteria reduce acidity in phagosome and a cell wall component (i.e. lipoarabinomannan) impairs Caþ/calmod ulin pathway thus inhibitingL phagosome-lysosome fusion. Following successful arrest of phagosome maturation, the multiplication of bacilli begins and the macrophage even tually ruptures to release its bacilli, which are taken up by macrophages and continues infection cycle further expanding the spread.[8] Fig No 1. Image shows general symptoms of Tuberculosis. [5]

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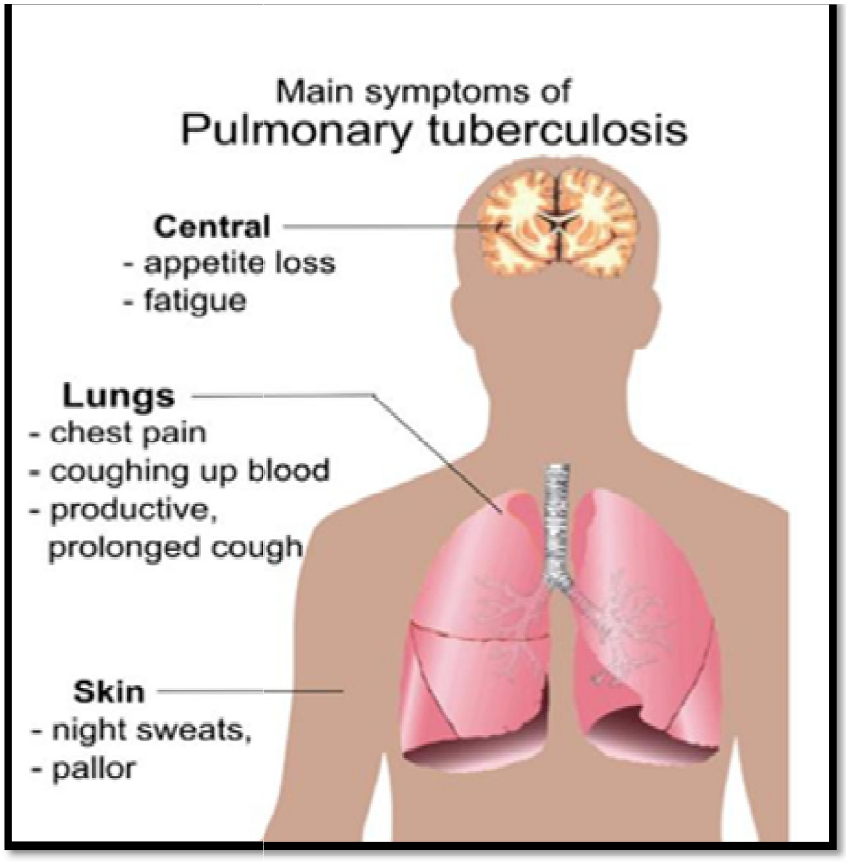

Fig No 1. Image shows general symptoms of Tuberculosis. [5]

CHALLENGES IN TUBERCULOSIS DIAGNOSIS AND TREATMENT

The therapeutic approach for DR-TB and the prognosis thereof is significantly corre lated to the resistance pattern; however, the clinical management of DR-TB is generally complicated. Multidrug-resistant TB (MDR-TB) is defined as resistance to INH and RIF, the two most powerful front-line anti-TB drugs. In 2021, there were an estimated 450,000 MDR-TB incidentcases. Thecurerates for MDR-TBaretypicallysignificantly lower than DS-TB.[30]The 2019 WHO recommended second-line regimen for MDR-TB is an 18–20 months treatment protocol, contingent on the patient's response to therapy. The MDR-TB medication regimen consists of at least four drugs in the intensive phase: three drugs from group A [linezolid, bedaquiline (BDQ) and moxifloxacin/levofloxacin] and one drug from group B (clofazimine, or terizidone/cycloserine).[9]

LAB DIAGNOSIS (MODERN METHOD):

There is a movement in clinical laboratories away from the conventional time consuming and tedious test for species identification of Mycobacteria recoveredinculture e.g.nucleic acid probes have been produced to identify MTB, Mycobacte rium avium intracellulare, M. kansasii and M. gordonae. There are 4 major applications used in clinical laboratories.

Use of DNA probes for culture confirmation of isolates recovered from clinical specimens.

Use of DNA sequencing for identification of mycobacteria.

Use of nucleic acid amplification tests (NAAT) for direct detection of MTB from clinical specimens.

DNA finger printing and strain typing of mycobacterium species.[10]

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NOVEL DRUG USED FOR TUBERCULOSIS TREATMENT

Bedaquiline:

It belongs to Group D add on agents specifically D2 category. It also a non-part of the core MDR TB regimen (WHO Report). It is a diarylquinoline bactericidal anti mycobacterial drug mainly used in adults with other anti bacterials to treat pulmonary TB. ATP synthase is the enzyme involved in the generation of energy through ATP. Bedaquiline inhibits the ATP synthase of proton pump of Mycobacterium, resulting in the death of bacteria.[11]

Delamanid:

Delamanid belongs to Group D add on agents specifically D2 category. It also non-part of the core MDR TB regimen. Delamanid is derived from nitro-dihydro imidazooxazole class of compounds that are known to interfere with mycolic acid synthesis and hence used in multidrug and extensively drug resistant TB, in regimen comprising of other antibiotics. It's developed and marketed by Otsuka Pharmaceutical Co., Ltd (Tokyo, Japan) (Drugbank).[12]

Sutezolid (PNU-100480):

It is a thiomorpholinyl analog of linezolid with preliminary evidence for superior efficacy against M. tuberculosis. In the mouse model, sutezolid shortens standard treatment by 1 month, whereas linezolid does not in the whole blood culture model, the maximal bactericidal activity of sutezolid (20.42 log/day) is more than twice that of linezolid.[13]

Diarylquinoline antibiotics

The proton pump activity of MTB adenosine triphosphate synthase can be inhibited by 1.2-diarylquinoline antibiotics. Among them, bedaquiline (Bdq) is the most representative.It is a concentration dependent novel 1.2-diarylquinoline antibiotics.[14]

MARKETED FORMULATION OF ANTI-TUBERCULOSIS DRUG:

The management of tuberculosis relies on several marketed formulation developed by pharmaceutical companies to ensure pateint-friendly dosing, improved stability, and wide accessiblity. First-line anti-tb drug such as isoniazid, rifampicin, ethambutal, and pyrazinamide are available under various brand names – for example, Isonex(Lupin), Rimactane(Novartis), Myambutol(Lupin), and Pyazine(Lupin).These formulations are commonly supplied as tablets or capsules, making them suitable for daily administration.

Sirturo (Bedaquiline)

Bedaquiline inhibits mycobacterial ATP (adenosine 5'-tri conversion (SCC), defined as the interval in days between the first dose of the study drug and the date of the first of two consecutive negative sputum cultures collected at least 25 d apart during treatment. Results from the first trial showed that patients treated with Sirturo combination therapy achieved SCC in a me dian time of 83 d, compared with 125 d in patients treated with placebo combination therapy. According to these results, 77.6% of patients in the treatment group reached treatment success after 24 wk compared with 57.6% of those in the placebo group. Results from the second trial showed the median time to SCC was 57 d, supporting the efficacy findings of the first trial.[15]

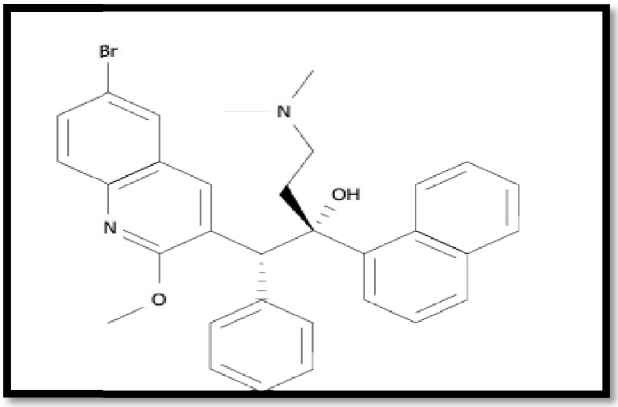

Fig No 2. CHEMICAL CONSTITUTION OF SIRTURO (BEDAQUILINE).[16]

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CIINICAL APPLICATION OF NOVEL ANTITUBERCULOSIS DRUG IN MULTI-DRUG RESISTANCE TUBERCULOSIS:

With the continuous emergence of novel antituberculosis chemotherapy drugs, many clinical trials have explored new treatmentstrategiesforMDR-TB.Theaimistoenhancetreatment success rates, improve tolerability and safety, and shorten the duration of drug-resistant TB chemotherapy.(17)

Ultra-short-course fully oral chemotherapy regimen:

Several studies have evaluated ultra-short-course regimens that are fully oral (without the use of injectable aminoglycosides) and have shown promising therapeutic outcomes and favorable drug safety profiles.(9) As a result, the 2022 WHO guidelines for the treatment of MDR-TB have undergone signifi cant changes, recommending the adoption of ultra-short-course fully oral chemotherapy for patients with drug-resistant and fluoroquinolone-resistant TB.(17)

Chemotherapy new regimens under clinical trials:

Combinations of novel antituberculosis drugs are currently being evaluated in various research studies and trials [84]. Here, we will discuss these new regimens and their prospects. The NExT Study (NCT02454205) [81] is a multicenter random ized controlled trial conducted on adult patients with MDR-TB (those resistant to fluoroquinolones or aminoglycosides). The results showed that a fully oral 6-month regimen (including three drugs from WHO Category A and two drugs from Category B or C) demonstrated superior treatment effectiveness and safety compared with a 9-month injectable regimen (without the use of Lzd or Bdq).(18)

MANAGEMENT OF TUBERCULOSIS:

Although frequently diagnosed in hospital, TB is largely managed in the outpatient setting. With the high proportion of people with TB also having advanced age or co-morbidities, however, complex disease is common, and may require management in hospital. People with TB requiring hospitalization should be admitted to institutions with adequate airborne isolation rooms and with providers experienced in TB management.(32) Interruptions are common in treatment of TB disease. Generally speaking, treatment interruptions are more con cerning in people with extensive disease (eg, smear positive, cavitary or disseminated disease) and in people with advanced immune suppression (eg, untreated HIV). Treatment inter ruptions are also more concerning during the intensive phase, when uninterrupted treatment is needed to achieve a rapid reduction in bacillary burden. Reinstituting therapy after treat ment interruption should be performed in consultation with the patient and a TB expert. It is based on expert guid ance and modified from existing guidelines and protocols.(19)

SIGNIFICANCE OF TB MANAGEMENT:

New diagnostic tools are particularly await ed in order to improve the diagnosis of disease and latent infection, the rapid detection of drug-resistance, and for use in the pediatric population. Several new diagnostics or diag nostic methods have been endorsed by the WHO since 2007 and many others are under investigation. this approach may be potentially useful togeth er with routine diagnostic tests in order to build up individualized therapeutic schemes in severe cases of MDR-TB and extensively drug resistant TB (XDR-TB).(35) Vaccines may eventually be the most effective response to TB but the development of effec tive vaccines is considerably hindered by the complex biology of mycobacteria, whose nature is still partially undefined.(20)

II. CONCLUSION

Tuberculosis remains a deadly disease throughout the world. Many efforts to remove TB have been hampered due to poverty, lack of health care access, drug resistance, immunosuppressed populations (e.g. HIV infected persons, Diabetes patient or any other infection) and global migration. Effective management is carried out by using a combination of clinical, radiographic, microbiological, histopathologic methods and initiation of appropriate multidrug therapy. In addition to the effective treatment of patients with active TB, public health management strategies include diagnosis, contact investigation, and testing of persons who came into close contact with patients with active TB. The increasing population, poverty, improper treatment is the main reason behind the growth of TB. Short course

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chemotherapy has been considered to be very effective and fruitful in the treatment of TB. Some mandatory steps might be taken to minimising the resistance problem in antitubercular drugs and to provide better efficacy and potent therapeutic effect.

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